The Screened Coulomb Potential (SCP) Continuum Solvent Model for Macromolecules

For an arbitrary distribution of N charges q_i at positions $\mathbf{r}_i$ the electric field $\mathbf{E}(\mathbf{r})$ at any position $\mathbf{r}$ is given by

$$\mathbf{E}(\mathbf{r}) = \sum_{i=1}^{N} \frac{q_i(\mathbf{r}-\mathbf{r}_i)}{\varepsilon(\mathbf{r})|\mathbf{r}-\mathbf{r}_i|^3} \qquad (1)$$

and it is always possible to define the potential $\phi(\mathbf{r})$ at position $\mathbf{r}$ as

$$\phi(\mathbf{r}) = \sum_{i=1}^{N} \frac{q_i}{D(\mathbf{r})|\mathbf{r}-\mathbf{r}_i|} \qquad (2a)$$

where the physically measurable dielectric function $\varepsilon(\mathbf{r})$ and the mathematical function $D(\mathbf{r})$ are related by the definition of electric potential $\mathbf{E}(\mathbf{r}) = -\nabla_{\mathbf{r}}\phi(\mathbf{r})$ Note, for example, that for one particle in pure solvent (i.e., spherical symmetry) the relationship between the two quantities is given by

$$\varepsilon(r) = D(r)\left[1 + \frac{r}{D(r)}\frac{d}{dr}D(r)\right]^{-1} \quad (3)$$

Derivation of the SCP-ISM

The complete formulation of the SCP-ISM was reported in [1,2]; here the derivation presented in [2] will be outlined. Figure 1 presents a schematic diagram of the thermodynamic cycle used for building the system (macromolecule immersed in the solvent). The basic assumption in this derivation is that the screening function (which is position-dependent and for which the exact form is in general unknown) is approximated as a distance-dependent function and then the potential of Eq.(2a) is written as

$$\phi(\mathbf{r}) = \sum_{i=1}^{N} \frac{q_i}{D(|\mathbf{r}-\mathbf{r}_i|)|\mathbf{r}-\mathbf{r}_i|} \quad (2b)$$

At the present stage of development the SCP-ISM is a "first order" model that requires refinement ("higher orders" corrections) by introducing an explicit position dependency of the screening function (this is part of an ongoing effort and a preliminary description of this correction is reported in Refs.[18,19]) [note, however, that in an indirect way the total screening $D(\mathbf{r})$ *is*, actually, a complex function of the position, in the same sense that

Coulomb's law is for an arbitrary distribution of charges, because comparison of Eqs.(2) leads to $D(\mathbf{r}) \sim \left[\sum_i q_i / |\mathbf{r} - \mathbf{r}_i| \right] / \left[\sum_i q_i / |\mathbf{r} - \mathbf{r}_i| D(|\mathbf{r} - \mathbf{r}_i|) \right]$.

From the upper panel, the total electrostatic energy E_T is given by

$$E_T = \Delta W_{1 \to 2} + \Delta W_{2 \to 3} \quad (4)$$

where the first term is the energy required to construct the molecule in the vacuum, and the second term is the polar component of the solvation energy ΔG_s^{pol}.

The process of bringing a particle from (1) to (2) is thought of as a typical solvation process where the particle is transferred from vacuum to an effective (or virtual) solvent composed of the growing molecule in vacuum (at any given point in the process the growing molecule is a dielectric medium even when it is surrounded by vacuum). This effective medium is characterized by a dielectric function $\varepsilon_v(r)$ or by its related screening function $D_v(r)$, where the index v indicates that the molecule is in vacuum. This dielectric (or screening) function accounts for the average effects of all the possible screening mechanisms in the system composed of the macromolecule *in the vacuum.*

Similarly, in bringing particles from (1) to (3) each particle is solvated into an effective medium composed by the growing macromolecule in the solvent. Here too the effective medium is characterized by a dielectric function $\varepsilon_s(r)$ or by its related screening function $D_s(r)$, where the index s indicates that the molecule is immersed into the solvent. As before, this dielectric (or screening) function accounts for the average effects of all the possible screening mechanisms in the system composed of the macromolecule *in the solvent.*

Therefore, to calculate E_T and ΔG_s^{pol} it is necessary to evaluate explicitly $\Delta W_{1 \to 2}$ and $\Delta W_{1 \to 3}$. For
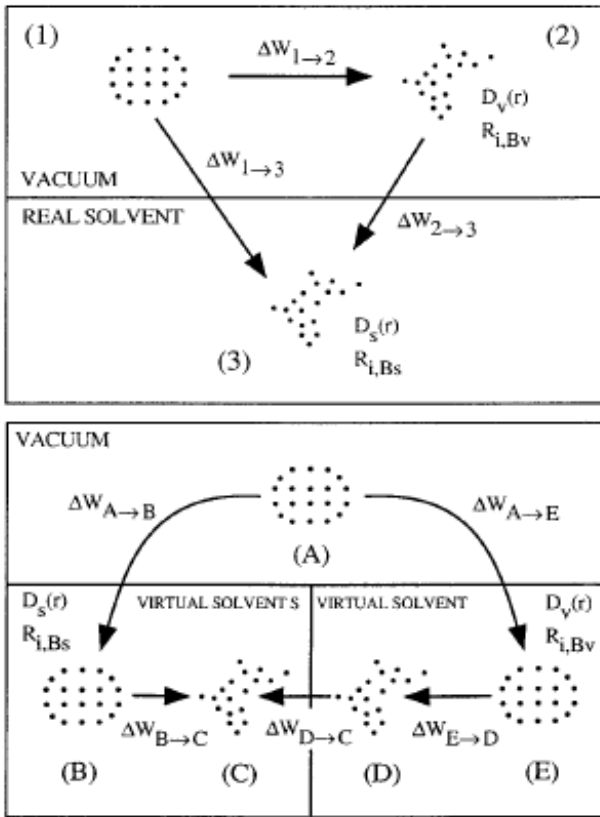

Figure 1

this we resort to the decomposition shown in the lower panel of Figure 1. In this expanded thermodynamic cycle the two defined virtual solvents, s and v, are the ones described above, i.e., the effective dielectric media defined by the macromolecule within the solvent and in vacuum, respectively. From the energetic point of view the system in (2) or (3) (upper panel) is equivalent to the system in (D) or (C) (lower panel), respectively. Therefore,

$$\Delta W_{1 \to 2} = \Delta W_{A \to E} + \Delta W_{E \to D} \quad (5a)$$

$$\Delta W_{1 \to 3} = \Delta W_{A \to B} + \Delta W_{B \to C} \quad (5b)$$

The calculation of E_T requires the evaluation of the four terms at the right hand side of Eqs.(5). These terms are given by

$$\Delta W_{A \to B} = \sum_{i=1}^{N} \Delta W_{v,i}; \quad \Delta W_{A \to E} = \sum_{i=1}^{N} \Delta W_{s,i} \quad (6a)$$

$$\Delta W_{B \to C} = \frac{1}{2} \sum_{i \ne j}^{N} \Delta W_{v,ij}; \quad \Delta W_{E \to D} = \frac{1}{2} \sum_{i \ne j}^{N} \Delta W_{s,ij} \quad (6b)$$

In these equations $\Delta W_{v,i}$ is energy required to transfer particle i from (A) to (E), i.e., the solvation energy of i in the virtual solvent v; $\Delta W_{v,ij}$ is the work necessary to bring particle i and j from infinite separation to their final relative positions within the solvent v; and similarly for $\Delta W_{s,i}$ and $\Delta W_{s,ij}$ but in the virtual solvent s.

Calculation of the Interaction Energy Terms

The energy terms $\Delta W_{v,ij}$ and $\Delta W_{s,ij}$ describe the work required to bring the particle j to its final position in the molecule, in the field generated by particle i, for the growing system immersed in the virtual solvent v or s, respectively, i.e.,

$$\Delta W_{ij} = -q_j \int_{\infty}^{r_j} \mathbf{E}_i(\mathbf{r}) \cdot d\mathbf{r} = \frac{1}{8\pi} \int \mathbf{E}_i(\mathbf{r}) \cdot \mathbf{D}_j(\mathbf{r}) dv \quad (7)$$

where $\mathbf{E}_i(\mathbf{r}) = q_i(\mathbf{r}-\mathbf{r}_i)/\varepsilon(|\mathbf{r}-\mathbf{r}_i|)|\mathbf{r}-\mathbf{r}_i|^3$ and $\mathbf{D}_j(\mathbf{r}) = \varepsilon(|\mathbf{r}-\mathbf{r}_i|)\mathbf{E}_j(\mathbf{r})$ (in the first integral $\mathbf{r}$ is the position of particle j in any point of the arbitrary trajectory along which the particle j is taken to the final position $\mathbf{r}_j$; the second integral is evaluated over all the space when particle i and j are located in their final positions in the macromolecule, i.e., $\mathbf{r}_i$ and $\mathbf{r}_j$).
Using Eq.(2b) valid for distance-dependent systems the line integral can be integrated exactly noting that

$$\frac{d}{dx}\left[\frac{1}{xD(x)}\right] = -\frac{1}{x^2 D(x)}\left[1 + \frac{x}{D(x)}\frac{d}{dx}D(x)\right] \quad (8)$$

and yields

$$\Delta W_{ij} = \frac{q_i q_j}{D(r_{ij})r_{ij}} \quad (9)$$

where $\Delta W_{v,ij}$ and $\Delta W_{s,ij}$ are obtained by specifying $D(r_{ij})$ as $D_v(r_{ij})$ or $Ds(r_{ij})$, respectively.

Calculation of the Self-Energy Terms

The energy ΔW_i requires for transferring a particle from vacuum to a polar liquid with dielectric $\varepsilon(r)$ is given by

$$\Delta W_i = \frac{1}{8\pi}\int \mathbf{E}_i(\mathbf{r}) \cdot \mathbf{D}_i(\mathbf{r})dv - \frac{1}{8\pi}\int |\mathbf{E}_i^0(\mathbf{r})|^2 dv \quad (10)$$

where $\mathbf{E}^0$ is the electric field created by the particle in vacuum; the integration is performed over all the space. Using Eqs.(2b) and (8), both integrals in Eq.(10) can be evaluated exactly and give

$$\Delta W_i = \frac{q_i^2}{2}\left[\frac{1}{R_i D(R_i)} - \frac{1}{R_i'}\right] \quad (11)$$

where R_i and R'_i are the characteristic radii of the particle in the solvent and in the vacuum, respectively (formally, the lower integration limit). Using the Born approximation it is now possible to write the solvation energy as

$$\Delta W_i = \frac{q_i^2}{2R_{i,B}}\left[\frac{1}{D(R_{i,B})} - 1\right] \quad (12)$$

where $R_{i,B}$ is the Born radius of the particle i. Therefore, the self-energies $\Delta W_{v,i}$ and $\Delta W_{s,i}$ are obtained by specifying the corresponding screening function in each medium.

Finally, the total electrostatic energy E_T of the macromolecule in the solvent is given by

$$E_T = \frac{1}{2}\sum_{i \neq j}^{N} \frac{q_i q_j}{D_s(r_{ij})r_{ij}} + \frac{1}{2}\sum_{i=1}^{N} \frac{q_i^2}{R_{i,Bs}}\left[\frac{1}{D_s(R_{i,Bs})} - 1\right] \quad (13)$$

and since the same reasoning applies to the formation of the molecule in the vacuum, i.e.,

$$E_T' = \frac{1}{2}\sum_{i \neq j}^{N} \frac{q_i q_j}{D_v(r_{ij})r_{ij}} + \frac{1}{2}\sum_{i=1}^{N} \frac{q_i^2}{R_{i,Bv}}\left[\frac{1}{D_v(R_{i,Bv})} - 1\right] \quad (14)$$

the polar part of the solvation energy of the macromolecule ΔG_s^{pol} is given by $E_T - E_T{}'$, i.e.,

$$\Delta G_s^{pol} = \frac{1}{2}\sum_{i\neq j}^{N} \frac{q_i q_j}{r_{ij}}\left[\frac{1}{D_s(r_{ij})} - \frac{1}{D_v(r_{ij})}\right] \tag{15}$$

$$+ \frac{1}{2}\sum_{i}^{N} q_i^2 \left\{ \frac{1}{R_{i,Bs}}\left[\frac{1}{D_s(R_{i,Bs})} - 1\right] - \frac{1}{R_{i,Bv}}\left[\frac{1}{D_v(R_{i,Bv})} - 1\right]\right\}$$

Qualitative Description of the SCP-ISM

Figure 2 illustrates, schematically, the conceptual difference of the SCP-ISM with respect to other approaches: Panel A shows a macroscopic body with dielectric constant ε_2 immersed in a medium of dielectric constant ε_1. For this macroscopic system a well-defined boundary is placed between the two media. The components of the electric and displacement fields satisfy the usual boundary conditions at the interface. As illustrated in panel B implicit models usually transfer this macroscopic view directly to the microscopic realm of macromolecules, including small peptides and even small organic molecules. Note, however, that 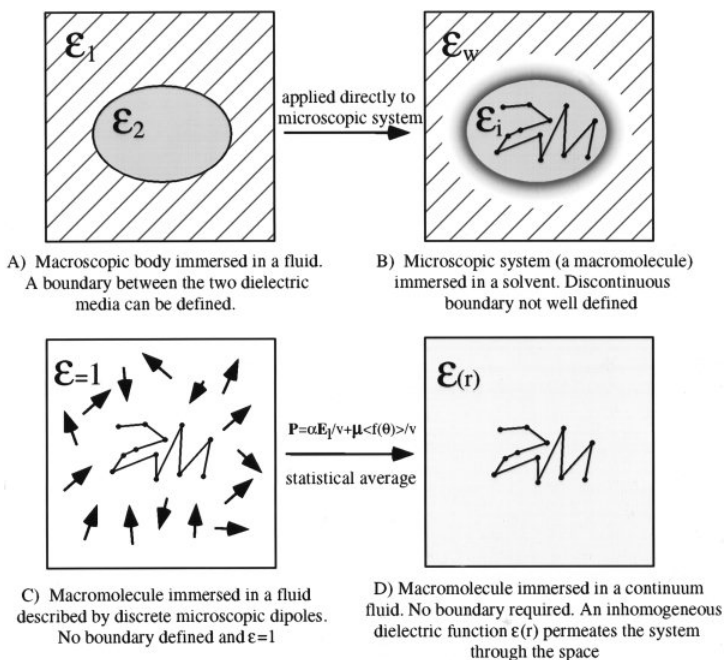the dielectric function increases slowly with the distance, as shown from basic theory and bulk dielectric value is reached at distances larger than 5-10 Å (see LDS theory and correction for Onsagre's reaction field). As shown in panels C and D, the derivation of the SCP-ISM follows an alternative path, making the transition from the microscopic to the macroscopic domain where an effective dielectric function permeates all of space. In this case the bulk dielectric value (or the so-

A) Macroscopic body immersed in a fluid. A boundary between the two dielectric media can be defined.

B) Microscopic system (a macromolecule) immersed in a solvent. Discontinuous boundary not well defined

C) Macromolecule immersed in a fluid described by discrete microscopic dipoles. No boundary defined and $\varepsilon=1$

D) Macromolecule immersed in a continuum fluid. No boundary required. An inhomogeneous dielectric function $\varepsilon(r)$ permeates the system through the space

Figure 2

called external dielectric ε_s) is reached only far from the protein, but becomes a more complex function as the distance to the protein decreases. In the SCP-ISM the reaction field is taken into account implicitly through the form of the screening function, which is obtained from experimental data and introduced in the parameters of the model.

Dielectric Properties and Screening Functions in Pure Liquids

What is $\varepsilon(r)$ in the case of an ionic or dipolar source immersed in a polar/polarizable medium such as water?

The answer is in the Lorentz-Debye-Sack theory of polar solvation that incorporates Onsager's reaction field corrections (neglecting other corrections). It can be shown that the screening function in the case of an ion is given by

$$\varepsilon(r) = 1 + \frac{\varepsilon_\infty - 1}{\varepsilon_\infty + 2}\left(\varepsilon(r) + 2\right) + \frac{4\pi\mu}{qv}r^2\varepsilon(r)L\left(\frac{q\mu\left(\varepsilon(r) + 2\right)}{(3kT + \mu R(r))r^2\varepsilon(r)}\right)$$

Iterative or numerical solution shows $\varepsilon(r)$ yields dielectric profiles with sigmoidal behavior in r. Therefore $D(r)$ is also sigmoidal in r. Figure 3 is taken from Ref.[1] where the dielectric profile of three liquids are shown along with the effects of Onsager's reaction fields.

Note that finding a first order differential equation with general sigmoidal solutions might be sufficient to obtain $D(r)$ analytically from Eq.(3). This equation was proposed and takes the form $dD(r)/dr = \lambda(1+D(r))(D_w-D(r))$ with solutions of the form $D(r)=(1+D_w)/[1+k\ \exp(-\alpha r)]-1$, where $k=(D_w-1)/2$ and the quantity $\alpha=\lambda(1+D_w)$ modulates the screening in the system, D_w is the static dielectric constant of the solvent.

Figure 3: dielectric profiles of acetamide, acetone and water, as calculated in Ref.[1].

The parameter α contains all the physics of the system; for pure liquids one value of α is shown to describe accurately the screening as defined by $\varepsilon(r)$ in Fig.3. Therefore, the SCP-ISM makes use of screening functions of the sigmoidal form with parameters α (to be adjusted as discussed in details in Ref.[1]) that describe all the screening mechanisms in the system. A protocol for calculating Born radii and corrections for Hydrogen-bonding (HB) strength are also reported in Refs.[1-4] (note that careful evaluation of the resulting HB stabilization is needed because of the new term E_T of Eq.(13) that replaces the Coulomb interaction in the original force-field as discussed in detail in Ref.[3])
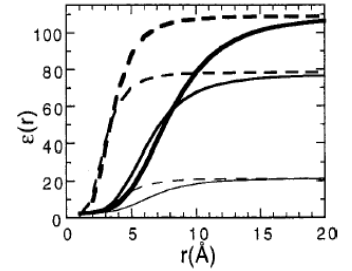
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